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Research paper

Evaluating the relationship between reelin gene variants (rs7341475 and rs262355) and schizophrenia: A meta-analysis

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HIGHLIGHTS

- The rs7341475 polymorphism in *RELN* gene was associated with decreased SZ risk.
- The rs262355 polymorphism was not associated with increased risk of SZ.
- The rs7341475 and rs262355 polymorphism was associated with SZ only in Caucasian.

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ABSTRACT

Studies have suggested that reelin (RELN) polymorphism was associated with the susceptibility of schizophrenia (SZ), but the results remained controversial. Thus, we conducted this meta-analysis to determine whether RELN variants (rs7341475 and rs262355) were associated with SZ risk. Studies were identified through retrieving Web of Science, PubMed and Embase databases from inception to May 2015. The genotype data were extracted to calculate the odds ratios (ORs) and 95% confidence intervals (CIs). For rs7341475, five studies with 4741 SZ patients and 10075 controls are included and the results indicate that carriage of A allele is associated with decreased SZ risk in dominant genetic model (OR = 0.90, 95%CI = 0.83–0.98) and additive model (OR = 0.90, 95% CI = 0.84–0.97). Subgroup analysis indicates that the association between rs7341475 and SZ is only significant in Caucasian. For rs262355, four studies with 2017 SZ patients and 3274 controls are included, the results demonstrate that carriage of A allele is associated with increased risk of SZ only in Caucasian (dominant model: OR = 1.17, 95%CI = 1.01–1.37; additive model OR = 1.13, 95%CI = 1.02–1.27). This meta-analysis suggests that rs7341475 (A/G) and rs262355 (A/T) polymorphisms in RELN gene are inversely associated with SZ risk.

1. Introduction

Schizophrenia, as one of the most common chronic psychiatric diseases, influences more than 1% of the population over the world [23]. However, the pathogenesis of schizophrenia still remains unclear. The main clinical manifestations of schizophrenia consist of hallucinations, delusions, impairment in social cognition, lacking interest and drive, and disorganized behavior [3]. It is suggested that both genetic background and environmental factors are involved in SZ [22]. Evidences from family or twin studies indicated that schizophrenia was a genetic disease and had a strong heritability [16]. Recent years, some genome-wide association studies (GWAS) were conducted to search the susceptibility genes or mutations for SZ and a few significant variants were observed [18]. Unfortunately, some of the variants were not confirmed by the latter genetic researches.

Reelin, mapping to chromosome 7q22, is one of genes that was identified to be associated with SZ risk [20]. RELN is a serine protease of the extracellular matrix and involved in signaling pathways underlying neurotransmission, memory formation and synaptic plasticity. It was reported that reelin could regulate microtubule function in neurons and neuronal migration by controlling cell–cell interaction [11]. Clinic studies suggested that the protein level of RELN in SZ patients was significantly lower than normal controls [8]. Evidences from some genetic studies indicated that single nucleotide polymorphism (SNP) could affect the transcription and translation activities of RELN gene, resulting in the lower

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expression of RELN. Many polymorphisms loci were identified in the *RELN* gene up to now, and the rs7341475 (G-A transition) and rs262355 (T-A transition) variants were most investigated [10,12,13,15,20,21]. Though many studies have been performed to explore the association between the RELN gene polymorphisms (rs7341475 and rs262355) and SZ risk, however, the results of them were still inconsistent [9,12,13,24].

Therefore, in order to determine the association between rs7341475 or rs262355 variants and SZ risk, we conducted this meta-analysis to summarize the controversial data.

2. Methods and materials

2.1. Literature search

To identify the eligible studies involved in the *RELN* polymorphisms and SZ, we performed a comprehensive search in the Web of Science, PubMed and Embase online databases using the following key words: *reelin*; *reln*; *polymorphism**; *variant**; and *Schizophrenia*. Only articles in English were included for further analysis.

2.2. Inclusion criteria and quality assessment

All studies included in this meta-analysis met the following inclusion criteria: a) case-control study evaluating the association between *rs7341475*or *rs262355*and SZ; b) genotype data are available; c) human studies; d) conform to Hardy–Weinberg Equilibrium (HWE).

The quality of each included articles was assessed by Newcastle-Ottawa Scale (NOS) [25]. This scale evaluated article quality from three aspects: selection, exposure and comparability. One score is given when one point is met and low score means bad quality.

2.3. Data extraction

To better present the characteristics of each study, the following information was collected: first author, year of publication, country, ethnicity, definition of SZ, genotyping methods and genotype distributions, number of patients and controls. Two authors extracted these data and input them into Excel file independently (Li Wei and Guo Xingzhi). Any disagreements were resolved through discussion (Xiao Shifu).

2.4. Data synthesis and statistical analysis

The ORs with 95% CIs were used to present the relationship between the *RELN* gene polymorphisms (rs7341475 or rs262355) and SZ risks. The dominant genetic model and additive model were used in this meta-analysis. The heterogeneity was measured by Cochran *Q* test and *I*-squared test ($P < 0.1$). The statistical models applied in calculating ORs were selected based on the result of heterogeneity test. A fixed-effects model was used when $P > 0.1$ or a random-effects model was applied when $P < 0.1$. Both Begg's and Egger's test were used to evaluate the publication bias. Furthermore, the sensitive analysis was performed by sequentially omitting a single study at one time. All the statistical analyses were performed using Revman 5.3 and Stata 12.0 software and $p < 0.05$ was considered to be significant.

3. Results

3.1. Search results and study characteristics

A computer based retrieving is performed in the Web of Science, PubMed and Embase databases, and 159 potential studies are identified. After importing into Endnote X software, 67 duplicate studies are excluded. After reviewing titles and abstracts, 65 studies are eliminated for they are reviews or not relevant to our analysis. 27 potentially relevant articles were reviewed for full-text analysis Fig. 1. Twenty studies are excluded: 16 articles for other diseases or SNPs, one with data unavailable [17] and three are not English [5,6,14]. Finally, a total of 7 studies are included in this meta-analysis and two of them evaluate both rs7341475 and rs262355 polymorphisms [9,12,13,15,20,21,24].

The detailed characteristics of each included studies are presented in Table1. The SZ patients are diagnosed according to Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition IV (DSM-IV) or Diagnostic and Statistical Manual of Mental Disorders – Third Edition Revised (DSM-III-R) diagnostic criteria.

For the rs7341475 polymorphism, 4741 SZ patients and 10075 controls from five studies are included to evaluate its association with SZ [12,13,15,20,21]. The genotype data from Shifman et al. study is divided into five parts according to different countries [20]. For the rs262355 polymorphism, 2017 SZ patients and 3274 controls from 4 studies are included in our meta-analysis [9,12,13,24]. The samples of Kahler et al. study were from three different countries, so we divide its genotype into three parts [9]. There are only two studies conducted in Asian for both rs7341475 polymorphism and rs262355 polymorphism.

3.2. Quantitative synthesis

No significant heterogeneity is found based on the results of Cochran *Q* test, so a fixed-effects model is applied for dominant model and additive model. For rs7341475 polymorphism, carriage of A allele is associated with decreased risk of SZ in both dominant model (AA + GA vs GG, OR = 0.90, 95% CI = 0.83–0.98) and additive model (A vs G, OR = 0.90, 95% CI = 0.84–0.97) Fig. 2. A subgroup analysis based on ethnicity is performed and the results suggest that rs7341475 polymorphism is significantly associated with reduced risk of SZ only in Caucasian (dominant model: OR = 0.88, 95%CI = 0.80–0.97; additive model: OR = 0.89, 95%CI = 0.82–0.96).

For rs262355 polymorphism, the pooled ORs suggest that the rs262355 polymorphism is not significantly associated with SZ risk in dominant (AA + GA vs GG, OR = 1.12, 95% CI = 1.00–1.26) and additive models (A vs G, OR = 1.07, 95% CI = 0.99–1.17) Fig. 3. However, subgroup analysis indicated that carriage of T allele is significantly associated with increased risk of SZ in Caucasian subgroup (dominant model: OR = 1.17, 95%CI = 1.01–1.37; additive model: OR = 1.13, 95%CI = 1.02–1.27). The sensitivity analysis is used to test the stability of the results. After omitting the study from Li et al., which is performed in Asian population, the results become significant. It is consistent to our subgroup analysis indicating that the association between rs262355 polymorphism and SZ is not significant in Asian population.

3.3. Assessment of publication bias

The potential publication bias is assessed by Egger's and Begg's tests. The Egger's test shows that *p* values of rs7341475 polymorphism for the dominant model and additive model are 0.016 and 0.012 respectively. The results indicate that there is potential publication bias in rs7341475 polymorphisms, which may be due to a lack of publication of small trials with opposite results or a flawed methodologic design in smaller studies. For rs262355 polymorphism, the Egger's test shows that the *p* values are 0.82 and 0.529 for dominant model and additive model. The median NOS score for rs7341475 and rs262355 are 5.5 and 6.0 respectively.